REMARKS

This is response to the Final Office action (Paper No. 20070926) mailed 2 October 2007 and to the Advisory Office action (Paper No. 20071023) mailed 30 October 2007. This Amendment is submitted with Request for Continued Examination.

Claims 1, 5-9, and 21-24 were pending in this application.

Claims 25 to 30 have been newly added.

Claim 1 has been amended to correct a typographical error. Claims 25 to 30 have been newly added by this supplemental amendment. The amendments are supported by the specification, for example, paragraph [0032] of the original specification. No new matter has been added.

No new matter has been added.

Three references are attached hereto in order to show that the examiner failed to show that there must be reasonable expectation of success, based on at least some degree of predictability.

I. Claim Rejections – 35 USC §103

A. Claim(s) 1, 7, 8, and 21-24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. (J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. (Journal of Forensic Science. March 1998. (43) 2, 431-434), in further view of Jurka (Nucleic Acids Research. 1993. Vol. 21. No. 9, 2252) as evidenced by Batzer et al. (Journal of Molecular Evolution. 1996. 42, 3-6).

The examiner failed to establish the *prima facie* case of obviousness because the above three basic criteria are not met.

MPEP §2142 states that:

> "If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner **must then consider any evidence** supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the applicant. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. 103, **the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not**." (Emphasis added).

1. There is no reasonable expectation of success in designing primers for the intra-*Alu* polymerase chain reaction amplification of an Alu element being more enriched in the human genome than in any non-human primate genome or present only in the human genome in order to achieve the same as or similar or better results to the Sifis et al.

There must be a reasonable expectation of success, based on at least some degree of predictability, at the time the invention was made. In the case of *Amgen , Inc. v. Chugai pharmaceutical Co.*, 927 F.2d 1200, 1207-08 (Fed. Cir.). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1 recites "said Alu element being more enriched in the human genome than in any non-human primate genome", claim 21 recites "said Alu element being present only in the

human genome", and claim 22 recites "a copy number of said predetermined genomic DNA in the human genome being higher than a copy number of said predetermined genomic DNA in any non-human primate genome".

The examiner argued that "a practitioner of ordinary skill in the art at the time of the invention wanting to quantify strictly human DNA from an unknown source through the method of Sifis would have been motivated to select an Alu known to reside strictly within the human genome to obtain accurate human results.

Since neither Sifis et al. nor Palmirotta et al. teach "Alu element being more enriched in the human genome than in any non-human primate genome" and "a copy number of said predetermined genomic DNA in the human genome being higher than a copy number of said predetermined genomic DNA in any non-human primate genome", the applicant assumed that the examiner's reasoning for "said Alu element being present only in the human genome" was also applied to the claims 1 and 22.

Here, there is no reasonable expectation of success, based on at least some degree of predictability.

Primer design has become a time-determining step in the workflow of high-throughout projects in life science laboratories. It is well known that the design of a PCR assay may involve tradeoffs among competing objectives, and extensive analysis is required. "Fine-tuning of PCR conditions is **not practicable for all target sequences** whenever a large number of genes of different lengths and GC content are to be amplified in parallel." (See Benita et al., Nucleic Acid Research, Vol.31 No. 16, abstract, which is attached hereto as Appendix I.) "**[I]t is known that DNA template with a very high or very low GC/AT ratio can be difficult to amplify**." (See

Id at col. 2.) "Most Alu elements located in the primate genomes that have been sequenced (e.g., human, chimpanzee, and rhesus macque) exist in high-GC content regions [3-5] and **also have high GC content** (an average of ~62.7%)", citing Quentin Y, Nucleic Acid Res. 20: 487-493. (See Han et al., PLOS genetics, vol. 3, p 1939-1949, 1943, which is attached hereto as Appendix II..) In designing primers, "base composition should be 50-60% (G+C)". (See Molecular Biology Techniques Manual, Third Edition, Edited by Vernon E Coyne, M Diane James, Sharon J Reid and Edward P Rybicki, available at http://www.mcb.uct.ac.za/pcroptim.htm, which is attached hereto as Appendix III.)

For the clarification of the examiner's position, the applicant respectfully asks that the examiner's position is consistent with the evidence, and that if there is a known sequence, the design of the primers for the polymerization is well within the ordinary skilled person in the art even if there is high GC content, in consideration of MPEP §2142

The instant application also specifically recognizes that "The need to incorporate subfamily specific diagnostic mutations into the primer design, as well as the high intrinsic GC content of *Alu* repeats, made it challenging to identify oligonucleotide primers acceptable to the design software packages."

That is, in view of evidence, there is no reasonable expectation of success that primers for the intra-Alu polymerase chain reaction amplification to quantitate a human DNA can be designed.

The examiner merely argued without some degree of predictability that if there is a certain target sequence, PCR can be practicable to the target sequence. "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be

some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (CAFC, 2006).

Furthermore, claims 23 and 24 recite that "each of said primers includes a subfamily-specific diagnostic mutation." In addition to the high GC content, the need to incorporate subfamily specific diagnostic mutations into the primer design make it more difficult to design primers acceptable to quantitate human DNA.

For example, as shown in Fig. 2, the primers themselves include the subfamily-specific diagnostic mutations. The *primers* may be designed without including subfamily-specific diagnostic mutations in the primer sequences themselves, whereas the *amplified products* amplified by the primers are likely to include subfamily-specific diagnostic mutations. The examiner did not provide why the ordinary skilled person in the art would incorporate the subfamily-specific diagnostic mutations are incorporated into the primer sequences. As stated above, the subfamily-specific diagnostic mutations can be merely incorporated into the amplified products, but not into the primer sequences.

The examiner merely argued that "it would have been further prima facie case obvious to a practitioner of ordinary skill in the art at the time of the invention to incorporate primers that are complementary to the specific Alu sequence." "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (CAFC, 2006).

For the foregoing reasons, claims 1, 7, 8, and 21-24 are patentable.

B. Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis *et al.* (J Forensic Sci. 2002 May; 47(3): 589-92) in view of Palmirotta *et al.* (Journal of Forensic Science. March 1998. (43) 2, 431-434), in further view of Jurka (Nucleic Acids Research. 1993. Vol. 21. No. 9, 2252), as evidenced by Batzer et al. (Journal of Molecular Evolution, 1996, 42, 3-6), and in further view of Buck *et al.* (BioTechniques. September 1999. 27: 528-536).

The examiner admitted that SEQ ID NOs:3 and 4 are not taught in Sifis et al. and Palmirotta et al, but are contained in Jurka.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie case obviousness. *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

1. The examiner's argument is at most that the references can be combined or modified. The examiner did not show the desirability of the combination.

First, the fact that the sequence is known does not mean that the DNA fragment is necessarily obvious.

The examiner's attention is invited to consider the following reference, <http://www.jpo.go.jp/shiryou_e/toushin_e/kenkyukai_e/contents.htm>. In the Comparative Study Report, the following question was given to US PTO:

"(1) Y : a structural gene encoding a functional polypeptide, the whole sequence of which is disclosed

Y' : a partial DNA fragment of Y

Does determination on novelty depend on whether the invention is claimed as "nucleotide" (chemical substance) or "probe" (use) ?" (See *Id.*)

The US PTO explained, based on the Patent Act, Sections 101, 102, 103 and 112, as follows:

> "The entire structural gene would not normally defeat the novelty of a fragment of that gene. However, claim language can be very important. If the fragment were claimed using open ended language such as "comprising," the claimed fragment could lack novelty. Thus, "a nucleotide sequence comprising Y' " would be anticipated by a structural gene that contained Y'.
>
> Under 35 U.S.C. Sec. 103 & l02(e), issued U.S. patents are considered prior art as of their filing date. Consequently, the answer is the same for (a) , (b) or (c).
>
> The answer is the same whether the invention is claimed as a chemical or as a probe. **However, claims directed to a method of using Y', even for open ended claim language such as "a method of using a probe comprising Y' " might be novel.**" (Emphasis added. See <ttp://www.jpo.go.jp/shiryou_e/toushin_e/kenkyukai_e/uspto/u50.htm>)

The examiner's position is inconsistent with the US PTO's position in the Report in our view. The applicant respectfully requests the examiner to clarify whether the examiner's position is consistent or inconsistent with the US PTO's position in the Report.

Second, with respect to the issue of reasonable expectation of success, the examiner improperly assumed that there was a reasonable expectation of success.

As stated above, "[I]t is known that DNA template with a very high or very low GC/AT ratio can be difficult to amplify." (See Appendix I attached hereto.) "Most Alu elements located in the primate genomes that have been sequenced (e.g., human, chimpanzee, and rhesus macque) exist in high-GC content regions [3-5] and also have high GC content (an average of ~62.7%)." Actually, the GC content of Alu Sb consensus shown in Fig. 1 in Jurka is more than 61%. In view of the evidence, there is no reasonable expectation of success that the more than the primers

having more than 60% GC content succeed in the desired amplification even if it is not impossible to have a successful primer having more than 60% GC in a certain target sequence. ("[B]ase composition should be 50-60% (G+C)." See Molecular Biology Techniques Manual, Third Edition; "PCR Primer Design and Reaction Optimization" available at http://www.mcb.uct.ac.za/pcroptim.htm, which is attached hereto as Appendix III.) In addition, the prior art teaches away from the primers of claim 5. As stated above, the prior art teaches that the GC content should not be more than 60%. However, the GC content of the primer of claim 5 is about 67% (28 GC /48).

Since there is no reasonable expectation of success and/or the prior art teaches away from the claimed invention, there is no prima facie case of obviousness.

2. There is no teaching in the prior art references about how to design the primers in order to achieve the same as or similar results to the Sifis et al

In Sifis et al., the SP primer pair was designed to amplify the core sequence of Alu in primate DNA. Protocols were optimized enabling the sensitive detection of DNA from 2.5-100pg. (See Abstract and co.2, second paragraph at page 590). However, there is no teaching in the prior art references about how to design the primers in order to achieve the same as or similar results to the Sifis et al. The prior art does not show the enablement. The examiner merely argued that Jurka taught that Sb2 is the youngest of all known human Alu subfamilies, and Jurka in combination with Sifis et al. and Palmirotta et al. does teach how to make the primers from Sb2 for the PCR protocol from which the amount of the human DNA can be quantitated as described in Sifis et al.

Moreover, the examiner improperly cited Buck. Please note that Buck compares the primers for the exact same 300-bp sequence *in automated DNA sequencing*, using the same PCR reaction condition. If the targets are different and/or the PCR reactions are different, and/or the purposes are different, the PCR primers will not yield the data of the same quality.

The examiner misunderstood Buck's teaching. Buck's teaching can be applied only to the case where the primers are for the exact same sequence in automated DNA sequencing.

For example, unlike Buck's teaching, different primers for the purpose of quantitation of human DNA result in different detection limits and different specificities, and, when there are primate DNA other than human DNA in a sample, different primers may result in different artifact Amplicons from DNA of other species as a result of sequence similarity to SINE elements from other species. Since the purpose of Buck et al. was automated DNA sequencing, these factors were not considered. It should be also noted that the design of a PCR assay may involve tradeoffs among competing objectives, and extensive analysis is required. The result for automated DNA sequencing cannot be applied to the human DNA quantitation method. For example, it is also evidenced by U.S. Pat. No. 7,026,120 disclosing that:

"it is well known that amplification primer sequences can be selected based upon computer comparisons of closely related sequences. Theoretically, sequences selected in this manner effectively should produce copies of the selected target sequence when employed according to nucleic acid amplification principles. Notwithstanding, the theoretical efficacy of sequences selected in the above manner, it is often times true that such sequences do not produce acceptable amounts of amplification product. Unfortunately, this phenomenon is not understood. Accordingly, while primers initially can be screened using computer programs efficacy cannot be adequately determined until such primers are employed in practice." (See Col. 1, lines 45-57.)

Also, the specification in the present application discloses that "the high Tm of the intra-Yb8 Alu-based primers was essential to the elimination of artifact amplicons from DNA of other species as a result of sequence similarity to SINE elements from other species." This problem is

not related to Buck wherein the 300 the primers for the exact same 300-bp sequence *in automated DNA sequencing*, using the same PCR reaction condition.

Buck et al. also acknowledged that, in their system, "the plasmid template was selected for absence of sequence extension obstacles and purified by double banding in CsCl-ethidium bromide isopycnic density gradients. Therefore, this template was extremely pure and optimal for sequencing. The primers were similarly highly purified. The reactions were performed in a single high-throughput sequencing facility under tightly controlled conditions. **Different results may be obtained using less carefully purified DNA templates with unusual sequences or structures or in less rigorously controlled sequencing operations**." (See page 535, last paragraph to page 536, first paragraph in Buck et al., emphasis added.) Accordingly, the teaching of Buck et al. can be applied only to the same reaction condition as described in Buck et al., and cannot be applied to the quantitation of human DNA in an unknown sample. It should be noted that Buck et al. is directed to a qualitative assay, whereas the present claims are directed to a quantitative assay.

The examiner did not consider the above teaching of Buck et al. The examiner's attention is also invited to consider Appendix III (Molecular Biology Techniques Manual, Third Edition; "PCR Primer Design and Reaction Optimization" available at http://www.mcb.uct.ac.za/pcroptim.htm), wherein the different primers result in different results (e.g., sensitivity).

The primers of claim 5 are not solely for automated DNA sequencing of a 300-bp test sequence as disclosed in Buck et al. Accordingly, it cannot be applied to the present application.

Please also note that "the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." (See MPEP §2142).

For the foregoing reasons, claim 5 is not obvious over the prior art.

C. Claim 9 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. in view of Palmirotta et al., in further view of Jurka as evidenced by Batzer et al. as applied to claim(s) 1, 7, 8, 21, and 22 above, and in further view of Gelmini et al. (Clinical Chemistry. 1997. 43:5, Pages 752-758).

Claim 9 depends from claim 1. Since claim 1 is patentable, claim 9 is also patentable.

A fee of $405.00 for **SMALL ENTITY** is incurred by the submission of the Request for Continued Examination (RCE) ($405.00). Should the other fees be incurred, the Commissioner is authorized to charge Deposit Account No. 02-4943 of Applicant's undersigned attorney in the amount of such fees.

In view of the above, all claims are submitted to be allowable and this application is believed to be in condition to be passed to issue. Reconsideration of the rejections is requested. Should any questions remain unresolved, the Examiner is requested to telephone Applicant's attorney.

Respectfully submitted,

Robert E. Bushnell
Attorney for the Applicant
Registration No.: 27,774

1522 "K" Street N.W., Suite 300
Washington, D.C. 20005
Tel. No. (202) 408-9040
Facsimile No. (202) 289-7100

Folio: P56885
Date: 1/2/2008
I.D.: REB/JHP